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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: 27 JULY 2007

SUBJECT: DIFENOCONAZOLE - Occupational and Residential Exposure/Risk Assessment for the Proposed New Uses of Difenoconazole on Fruiting Vegetables, Tuberous and Corm Vegetables, Pome Fruit, Sugar Beets and Ornamentals.

PC Code: 128847 DP Code: 340044

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INTRODUCTION

Under provisions in Section 3 of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), as amended, the Syngenta Crop Protection, Inc. has requested registration of the fungicide active ingredient (ai) difenoconazole for use on: fruiting vegetables (eggplant, groundcherry, pepino, pepper [includes bell pepper, chili pepper, cooking pepper, pimento, sweet pepper], tomatillo and tomato), pome fruit (apple, crabapple, loquat, mayhaw, pear, Oriental pear, quince), root and tuberous crops (arracacha, arrowroot, Chinese and Jerusalem artichoke, burdock, canna, bitter and sweet cassava, chayote, chufa, dasheen, ginger, leren, tanier, tumeric and yam [bean and true]), sugarbeets, and for use on ornamentals including residential landscapes.

This memorandum serves as the RD's assessment of exposure and risk to occupational pesticide handlers (mixers, loaders, applicators), to agricultural workers and to

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"homeowners". It should be noted that the risk assessment techniques used in this document are those that have been developed and refined by the Health Effects Division (HED)/Office of Pesticide Programs' Science Policy Council for Exposure (ExpoSAC). Therefore, the risk assessment methods are the same as those used by HED and are HED standard operating procedure (SOP).

USE PATTERN SUMMARY

The use pattern summary is taken from a draft label for the proposed product Inspire® Fungicide. Inspire® is not a currently registered product. Inspire® is a liquid formulation which contains 2.08 lb ai difenoconazole per gallon. The draft label indicates difenoconazole may be applied by ground machinery, aerially, via irrigation systems (chemigation) such as center pivot, solid set, hand moved, and moving wheel systems unless prohibited in the crop specific application directions.

The target pests are species of plant disease organisms in the genera: *Alternaria, Cercospera, Colletotrichum, Corynospora, Erysiphe, Fulvia, Gloeodes, Gymnosporangium, Leveillula, Mycosphaerella, Podosphaera, Schizothyrium, Septoria, Stemphylium, Venturia.* The pest organisms vary according to crop site. Not all pests occur on all sites.

Fruiting vegetables - Difenoconazole may be applied to fruiting vegetables aerially, with ground equipment (*i.e.* ground boom sprayer) and via chemigation. It should be applied in a minimum of 15 gallons of water per acre (gpa) by ground sprayer, aerially in a minimum of 5 gpa and in 0.1 - 0.25" water via irrigation. The rate of application is 4.0 - 7.0 fl oz formulation/A (0.07 - 0.11 lb ai/A). Applications should begin at the first signs of disease and should occur at 7 - 14 day intervals. There is a maximum application of 28 fl oz/A/crop (0.455 lb ai/a/crop) which equates to 4 applications/A/crop, at the high rate of application. It may be applied up to the day of harvest (0 day preharvest interval [PHI]). More than 2 consecutive sprays should not be applied without rotating to a fungicide with a different mode of action.

Pome fruit - Applications may be made aerially and by ground equipment (airblast sprayer). A minimum of 40 gpa is recommended for ground applications and 5 gpa by air. The rate of application is 2 - 4 fl oz/A (0.03 - 0.07 lb ai/A). Spray schedules vary according to pest species and may be 7 - 10 days or 10 - 14 days. Sprays may begin at green tip and continue through petal fall. The is a maximum application of 20.0 fl oz/A/crop (0.325 lb ai/A/crop) which equates to 5 applications/crop at the high rate. There is a 14 day PHI.

Root and tuberous vegetables - The rate of application is 4 - 7 fl oz/A (0.07 - 0.11 lb ai/A) and may be applied by ground machinery (ground-boom), aerially and via chemigation. Applications should begin at the first signs of disease. Ground applications should be made in a minimum of 15 gpa. Aerial applications should be made in a minimum of 5 gpa and via irrigation in 0.1 - 0.25 in water. There is a maximum

application of 28 fl oz/A/crop that may be applied (0.455 lb ai/A/crop). That equates to 4 applications/A/crop at the high rate of application. There is a 14 day PHI.

Sugarbeets - The rate of application is 4 - 7 fl oz/A (0.07 - 0.11 lb ai/A) and may be applied by ground spray (ground boom), aerially or via chemigation. It should be applied in a minimum of 15 gpa by ground, in a minimum of 5 gpa by air or in 0.1 - 0.25" water via irrigation. There is a maximum of 28 fl oz/A/crop (0.455 lb ai/A/crop) which equates to 4 applications/A/crop at the high rate of application. There is a 7 day PHI.

Ornamentals - The draft label states: "For outdoor application to ornamentals by commercial and non-professional (i.e., homeowner) applicators. May be used to apply to ornamentals around residential landscapes." The label lists carnation, iris, gladiolus and roses as specific use sites. The rate of application ranges from 2 - 8 fl oz/A (0.03 - 0.13 lb ai/A). Applications should be made on a 7 - 10 day schedule. There is a maximum of 32.0 fl oz/A/year (0.56 lb ai/A/yr) which equates to 4 applications/A/yr at the highest rate of application.

The label does not specify methods of application for ornamentals. ARIA/RD believes typical methods used to treat ornamentals will include garden hose-end sprayer, "pump-up" sprayer, backpack sprayer, and commercial hand-wand sprayers.

The draft label states that mixers, loaders, applicators and all other handlers must wear: long-sleeved shirt, long pants, shoes plus socks, chemical resistant gloves such as barrier laminate, butyl rubber greater than or equal to 14 mils, nitrile rubber greater than 14 mils or viton greater than 14 mils and protective eyewear.

See Table 1.0 for a summary of the proposed use pattern.

Table 1.0 Summary of Proposed Use Pattern for Difenoconazole	
Crop/Site	Fruiting vegetables Pome fruit Root & tuberous vegetables Sugarbeets Ornamentals (carnation, gladiolus, iris, roses)
Pest	numerous plant pathogens
Method of Applic.	ground-boom, airblast, aerial, hose-end, pump sprayer, backpack sprayer, spray-wand
Max. Applic. Rate	Fruiting vegetables - 0.11 lb ai/A Pome fruit - 0.07 lb ai/A Root & tuberous vegetables - 0.11 lb ai/A Sugarbeets - 0.11 lb ai/A Ornamentals (carnation, gladiolus, iris, roses) - 0.13 lb ai/A
Max. No. Applications	Fruiting vegetables - 4 Pome fruit - 5 Root & tuberous vegetables - 4 Sugarbeets - 4 Ornamentals (carnation, gladiolus, iris, roses) - 4
Applic. Interval	Fruiting vegetables 7 - 14 days Pome fruit 7 - 10 days and 10 - 14 days depending on pest Root & tuberous vegetables 7 - 14 days Sugarbeets 7 - 28 days Ornamentals 7 - 10 days
Preharvest Interval	Fruiting vegetables - 0 day Pome fruit - 14 day Root & tuberous vegetables - 14 day Sugarbeets - 7 day Ornamentals n/a
Restricted Entry Interval	the label lists 12 hours
Manufacturer	Syngenta

OCCUPATIONAL PESTICIDE HANDLER EXPOSURE

Based upon the proposed use patterns, ARIA/RD believes the most highly exposed occupational pesticide handlers will be mixer/loaders using open pour loading of liquids and applicators using ground-boom spray machinery, airblast sprayer, fixed-wing aircraft, garden hose-end sprayer, "pump-up" (compressed air) sprayer, backpack sprayer and high pressure hand-wand sprayer.

Application through irrigation systems is also permitted (chemigation). However, ARIA/RD believes an individual preparing an irrigation system to apply difenoconazole will not be more highly exposed than a mixer/loader using open-pour loading in support of aerial operations. There is typically no mixing and loading for application through irrigation systems. A handler prepares siphon tubes that will withdraw concentrate from its original container and meter it into the irrigation stream. There is no mixing or pouring in the sense of preparing dilute sprays for use in ground-boom, airblast or for aircraft application. Therefore, the estimated exposure for a mixer/loader is believed to

be greater than that for chemigation and thus protective for individuals involved in chemigation.

ARIA/RD believes pesticide handlers will be exposed to short-term duration (1 - 30 days) exposures, but not to intermediate-term (1 - 6 months) duration exposures. Although multiple applications are possible, they are separated by 10 - 14 day retreatment intervals. No more than 2 consecutive applications should be made. It is unlikely that pesticide handlers would be exposed continuously for 30 days or more.

In this case however, the short-term and intermediate-term toxicological endpoints are the same. Therefore, the assessment of short-term exposure and risk is adequate to describe risk from an intermediate-term exposure, should that occur.

Particularly for ground applications, private (*i.e.,* grower) applicators may perform all functions, that is, mix, load and apply the material. The HED ExpoSAC SOP Number 12 (29 March 2000) directs that although the same individual may perform all those tasks, they shall be assessed separately. The available exposure data for combined mixer/loader/applicator scenarios are limited in comparison to the monitoring of these two activities separately. These exposure scenarios are outlined in the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide (August 1998). HED has adopted a methodology to present the exposure and risk estimates separately for the job functions in some scenarios and to present them as combined in other cases. Most exposure scenarios for hand-held equipment (such as hand wands, backpack sprayers, and push-type granular spreaders) are assessed as a combined job function. With these types of hand held operations, all handling activities are assumed to be conducted by the same individual. The available monitoring data support this and HED presents them in this way. Conversely, for equipment types such as fixed-wing aircraft, ground boom tractors, or air-blast sprayers, the applicator exposures are assessed and presented separately from those of the mixers and loaders. By separating the two job functions, HED determines the most appropriate levels of personal protective equipment (PPE) for each aspect of the job without requiring an applicator to wear unnecessary PPE that might be required for a mixer/loader (*e.g.,* chemical resistant gloves may only be necessary during the pouring of a liquid formulation).

No chemical specific data were available with which to assess potential exposure to pesticide handlers. The estimates of exposure to pesticide handlers are based upon surrogate study data available in the PHED (August 1998). In certain cases, unit exposure data for a professional lawn care operator (LCO) is taken from: Memo, G. Bangs, 5 March 2003, MRID Nos 449722-01, 445185-01 and 444598-01 [DP barcode not stated].

For pesticide handlers, it is HED standard practice to present estimates of dermal exposure for "baseline" that is, for workers wearing a single layer of work clothing consisting of a long sleeved shirt, long pants, shoes plus socks and no protective gloves as well as for "baseline" **and the use of protective gloves** or other PPE as might be necessary. The label required PPE was discussed earlier.

As noted earlier, the use on ornamentals is intended for "homeowners" as well as by professional lawn care operators (LCO). The unit exposure data for "homeowners" is for persons wearing short pants and short-sleeved shirts as well as shoes plus socks. The unit exposures data for LCOs is for persons wearing a single layer of work clothing and protective gloves. For "homeowner" application, the area treated is assumed to be 0.5 acres per day. For an LCO, it is assumed that 5 acres are treated per day as multiple residences might be treated by a professional applicator.

Unit exposure information for "homeowners" is taken from 2 sources: 1) Draft Standard Operating Procedures for Residential Exposure Assessments (18 DEC 1997, page B-9) and 2) Memo, G. Bangs, 5 March 2003, MRID Nos 449722-01, 445185-01 and 444598-01 [DP barcode not stated]. In some cases, unit exposure data for a LCO is also taken from the 5 March 2003 memo by Bangs.

The MRIDs noted above are from the Outdoor Residential Exposure Taskforce (ORETF) and are proprietary and subject to data compensation. As such the data may only be used to the benefit of members of the ORETF. Syngenta is a member in good standing of the ORETF.

In July, 2007, the RAB1 toxicology team met to reconsider the toxicological database with regards to difenoconazole. At that meeting revisions were made to previous understandings of the toxicological data. The RAB1 toxicology team identified short-term (1 - 30 days) and intermediate-term (1 - 6 months) dermal toxicological endpoints. They were identified from a rat feeding study where the effects seen were reduced body weight gain in the F_0 females prior to mating, gestation and lactation. The No Observable Adverse Effect Level (NOAEL) for short- and intermediate-term duration exposures is 1.25 mg ai/kg bw/day. Since the NOAEL is from an oral study, a 15.3 % dermal absorption factor was applied.

Short-term and intermediate-term inhalation NOAELs (1.25 mg ai/kg bw/day) were identified from the same study. HED and RD assume 100 % absorption via the inhalation route of exposure. Since the dermal and inhalation endpoints are the same and are identified from the same study, the dermal and inhalation exposures are summed to determine the Margin of Exposure (MOE).

The HED Cancer Peer Review Committee (CPRC) has classified difenoconazole as a Group C possible human carcinogen. However, the committee recommended using the MOE approach for assessment (Memo, J.Rowland and E. Rinde, 7/24/94; Memo, P. Shah, 3 March 2007, HED Doc. No. 0054532). However, the Agency has not determined an acceptable level of concern using the MOE approach. In addition, exposures are not expected to be chronic in nature. Therefore, a cancer risk assessment was not conducted.

See the ATTACHMENT for a summary of toxicological endpoints used for risk assessment. Table 2.0 provides a summary of estimated exposures and risks to occupational pesticide handlers.

Included in Table 2.0 are the following occupational pesticide handler scenarios:
1) Mixer/loaders using open pour loading of liquids (PHED);
2) Applicator using open-cab ground-boom sprayer (PHED);
3) Applicator using open-cab airblast sprayer (PHED);
4) Aerial applicator (PHED)
5) Mixer/Loader/Applicator using "pump-up" compressed air sprayer (ORETF);
6) Mixer/Loader/Applicator using backpack sprayer (PHED); and
7) Applicator using high-pressure hand-wand sprayer (PHED).

Also assessed are persons, "homeowners" who apply the material to residential ornamental plantings. "Homeowners" are assessed wearing short sleeved shirts, short pants and shoes plus socks.
Homeowner scenarios assessed are:

1) Mixer/Loader/Applicator using garden hose-end sprayer (ORETF study OMA 004);
2) Mixer/Loader/Applicator using "pump-up" compressed sprayer (ORETF study OMA 006); and
3) Mixer/Loader/Applicator using backpack sprayer (PHED).

See Table 3.0 for assessments of exposure and risk to "homeowner" pesticide handlers.

Table 2.0 Summary of Exposure & Risk for Occupational Handlers Applying Difenoconazole				
Unit Exposure[1] mg ai/lb handled	Applic. Rate[2] lb ai/unit	Units Treated[3]	Avg. Daily Exposure[4] mg ai/kg bw/day	Short-term MOE[5]
Mixer/Loader Using Open Pour Loading of Liquids				
Dermal: SLNoGlove 2.9 HC SLWithGlove 0.023 HC Inhal. 0.0012 HC	0.11 lb ai/A	350 A/day	Dermal: SLNoGlove 0.244 SLWithGlove 0.0019 Inhal. 0.00066	 5 488
Applicator Using Open-Cab Ground-boom Sprayer				
Dermal: SLNoGlove 0.014 HC SLWithGlove 0.014 MC Inhal. 0.00074 HC	0.11 lb ai/A	80 A/day	Dermal: SLNoGlove 0.000269 SLWithGlove 0.000269 Inhal. 0.000093	 3,453 3,453
Applicator Using Open-cab Airblast Sprayer				
Dermal: SLNoGlove 0.36 HC SLWithGlove 0.24 HC Inhal. 0.0045 HC	0.07 lb ai/A	40 A/day	Dermal: SLNoGlove 0.0022 SLWithGlove 0.00147 Inhal. 0.00018	 525 758
Aerial Applicator (Pilots not required to wear gloves)				
Dermal: SLNoGlove 0.0050 MC Inhal. 0.000068 MC	0.11 lb ai/A	350 A/day	Dermal: SLNoGlove 0.00042 Inhal. 0.000037	 2735
Mixer/Loader/Applicator Using "Pump-Up" Compressed Air Sprayer				
Dermal: SLWithGlove 0.33 **LCO** Inhal 0.0027	0.13 lb ai/A	5.0 A/day	Dermal: SLWithGlove 0.000469 Inhal. 0.000025	 2,530
Mixer/Loader/Applicator Using Backpack Sprayer				
Dermal: SLWithGlove 2.5 **LCO** LC Inhal. 0.03 LC	0.13 lb ai/A	5.0 A/day	Dermal: SLWithGlove 0.00355 Inhal 0.00028	 326
Applicator Using High-Pressure Handwand Sprayer				
Dermal: SLWithGlove 0.64 **LCO** LC Inhal. 0.079 LC	0.13 lb ai/A	5.0 A/day	Dermal: SLWithGlove 0.00091 Inhal. 0.000734	 760

1. Unit Exposures are taken from "PHED SURROGATE EXPOSURE GUIDE", Estimates of Worker Exposure from The Pesticide Handler Exposure Database Version 1.1, August 1998. Inhal. = Inhalation. Units = mg a.i./pound of active ingredient handled. Data Confidence: LC = Low Confidence, MC = Medium Confidence, HC = High Confidence. Unit exposures are also taken from ORETF studies OMA 004,OMA006 and from the Draft Residential SOPs, DECEMBER 1997. SLNoGlove = single layer of work clothing (long pants, long-sleeved shirt, shoes plus socks) and NO protective gloves. SLWithGloves = single layer work clothing AND WITH the use of protective gloves. SS & SP = short sleeved shirt and short pants. LS & LP = long sleeved shirt and long pants
2. Applic. Rate. = Taken from the draft Inspire® label.
3. Units Treated are taken from "Standard Values for Daily Acres Treated in Agriculture"; SOP No. 9.1. Science Advisory Council for Exposure; Revised 5 July 2000; and assumed for LCO treating ornamentals.
4. Average Daily Dose (ADD) = Unit Exposure * Applic. Rate * Units Treated * absorption factor (15.3 % for dermal) ÷ Body Weight (70 kg).

5. NOAEL = No Observable Adverse Effect Level (1.25 mg a.i./kg bw/day for short-term and intermediate-term dermal and inhalation)
6. MOE = Margin of Exposure = No Observable Adverse Effect Level (NOAEL) ÷ ADD. ADD = dermal + inhalation.

A MOE of 100 is adequate to protect occupational pesticide handlers from exposures to difenoconazole. Provided occupational handlers wear protective gloves, all MOEs are > 100 therefore these estimated exposures do not exceed ARIA/RDs level of concern.

Table 3.0 Summary of Exposure & Risk for Homeowners Applying Difenoconazole

Unit Exposure[1] mg ai/lb handled	Applic. Rate[2] lb ai/unit	Units Treated[3]	Avg. Daily Exposure[4] mg ai/kg bw/day	Short-term MOE[5]
Mixer/Loader/Applicator Using Garden Hose-end Sprayer				
Dermal: SS&SP 11 **homeowner** Inhal. 0.017	0.13 lb ai/A	0.5 A/day	Dermal: shrtsl&pants 0.00156 Inhal. 0.0000158	793
Mixer/Loader/Applicator Using "Pump-Up" Compressed Air Sprayer				
Dermal: SS&SP 38 **homeowner** Inhal 0.0027	0.13 lb ai/A	0.5 A/day	Dermal: shrtsl&pants 0.00539 Inhal. 0.0000025	231
Mixer/Loader/Applicator Using Backpack Sprayer				
Dermal: SS&SP 5.1 **homeowner** Inhal. 0.03	0.13 lb ai/A	0.5 A/day	Dermal: shrtslv&pants 0.000725 Inhal. 0.000028	1,660

1. Unit Exposures are taken from "PHED SURROGATE EXPOSURE GUIDE", Estimates of Worker Exposure from The Pesticide Handler Exposure Database Version 1.1, August 1998. Inhal. = Inhalation. Units = mg a.i./pound of active ingredient handled. Data Confidence: LC = Low Confidence, MC = Medium Confidence, HC = High Confidence. Unit exposures are also taken from ORETF studies OMA 004,OMA006 and from the Draft Residential SOPs, DECEMBER 1997. SLNoGlove = single layer of work clothing (long pants, long-sleeved shirt, shoes plus socks) and NO protective gloves. SLWithGloves = single layer work clothing AND WITH the use of protective gloves. SS & SP = short sleeved shirt and short pants. LS & LP = long sleeved shirt and long pants
2. Applic. Rate. = Taken from the draft Inspire® label.
3. Units Treated are taken the residential SOPs
4. Average Daily Dose (ADD) = Unit Exposure * Applic. Rate * Units Treated * absorption factor (15.3 % for dermal) ÷ Body Weight (70 kg).
5. NOAEL = No Observable Adverse Effect Level (1.25 mg a.i./kg bw/day for short-term and intermediate-term dermal and inhalation)
6. MOE = Margin of Exposure = No Observable Adverse Effect Level (NOAEL) ÷ ADD. ADD = dermal + inhalation.

A MOE of 100 is adequate to protect residential pesticide handlers from exposures to difenoconazole. MOEs are >100, therefore these estimated exposures do not exceed ARIA/RDs level of concern.

POST-APPLICATION EXPOSURE TO AGRICULTURAL WORKERS

It is possible for agricultural workers to have post-application exposures to pesticide residues during the course of typical agricultural activities. HED in conjunction with the Agricultural Re-entry Task Force (ARTF) has identified a number of post-application agricultural activities that may occur and which may result in post-application exposures to pesticide residues. HED has also identified Transfer Coefficients (TC) (cm^2/hr) relative to the various activities which express the amount of foliar contact over time, during each of the activities identified. For the proposed new crop use sites, the highest TC associated with fruiting vegetables is 1,000 cm^2/hr for hand harvesting, staking and training; for pome fruit is 3,000 cm^2/hr for thinning; for root and tuberous vegetables is 2,500 for hand harvesting; for sugarbeets is 1,500 for irrigation activities and scouting; and for floricultural crops is 5,000 cm^2/hr for hand harvesting, pinching and thinning. As a screening level assessment, ARIA/RD uses the most conservative TC, 5,000 cm^2/hr for floricultural crops at the 0.13 lb ai/A rate of application. The TC for floricultural activities is taken from Memo, T. Dole and M. Loyd, 11 August 2005, "Review of Determination of Dermal and Inhalation Exposure to Reentry Workers During Harvesting in Greenhouse Grown cut Flowers, MRID 465139-01, DP Barcode D319969, [ARTF Study No. ARF055]". The Dole/Loyd memo amends the SOP 3.1.

The TCs used in this assessment are from an interim TC Standard Operating Procedure (SOP) developed by HED's ExpoSAC using proprietary data from the ARTF database (SOP # 3.1). It is the intention of HED's ExpoSAC that this SOP will be periodically updated to incorporate additional information about agricultural practices in crops and new data on transfer coefficients. Much of this information will originate from exposure studies currently being conducted by the ARTF, from further analysis of studies already submitted to the Agency, and from studies in the published scientific literature.

Lacking compound specific dislodgeable foliar residue (DFR) data, HED assumes 20 % of the application rate is available as DFR on day zero after application. This is adapted from the ExpoSAC SOP No. 003 (7 May 1998 - Revised 7 August 2000).

The following convention may be used to estimate post-application exposure.

Average Daily Dose (ADD) (mg a.i./kg bw/day) = DFR $\mu g/cm^2$ * TC cm^2/hr * hr/day * 0.001 mg/µg * 1/70 kg bw

and where:

Surrogate Dislodgeable Foliar Residue (DFR) = application rate * 20% available as dislodgeable residue * $(1\text{-}D)^t$ * 4.54×10^8 µg/lb * 2.47×10^{-8} A/cm^2.

Floricultural post-application activities

0.13 lb a.i./A * 0.20 * $(1\text{-}0)^0$ * 4.54×10^8 µg/lb * 2.47×10^{-8} A/cm^2 = 0.29 $\mu g/cm^2$, therefore,

0.29 µg/cm^2 * 5,000 cm^2/hr * 8 hr/day * 0.001 mg/µg * 0.153 (15.3 % dermal absorption) ÷ 70 kg bw = 0.025 mg/kg bw/day.

MOE = NOAEL ÷ ADD then 1.25 mg/kg bw/day ÷ 0.025 mg/kg bw/day = **50.**

A MOE of 100 is adequate to protect agricultural workers from post-application exposures. The short-term duration MOE is < 100 and therefore exceeds ARIA/RDs level of concern. Post-application activities with a TC > 2,500 cm^2/hr will result in MOEs of concern.

HED assumes post-application dislodgeable foliar residue dissipates at a rate of 10 % per day. At that rate of dissipation, for floricultural activities with an application rate of 0.13 lb ai/A and a TC of 5,000 cm^2/hr, it is post-application day 10 before MOEs of 100 are attained. For floricultural activities, under these circumstances a restricted entry interval of 10 days is necessary to protect agricultural workers. Use of the lower rate of application (0.03 lb ai/A), results in MOEs that do not exceed levels of concern.

ARIA/RD notes that "homeowners"/residents would not be expected to be involved in harvesting, pinching or thinning ornamentals for 8 hours per day, as might agricultural workers. Further, as a matter of practice, HED typically assumes post-application exposure of homeowners to ornamentals is negligible due to the re-entry interval and to the premise that homeowners wouldn't be expected to be exposed to the same durations of exposures as might occupationally exposed persons.

Pome fruit post-application activities

For the proposed crop use sites, the crop with the next highest TC is pome fruit with a TC of 3,000 cm^2/hr for hand thinning. However, it should be noted that the rate of application to pome fruit is 0.07 lb ai/A as opposed to 0.13 lb ai/A for the ornamentals uses. Therefore:

0.07 lb a.i./A * 0.20 * $(1-0)^0$ * 4.54 x 10^8 µg/lb * 2.47 x10^{-8} A/cm^2 = 0.157 µg/cm^2 , therefore,

0.157 µg/cm^2 * 3,000 cm^2/hr * 8 hr/day * 0.001 mg/µg * 0.153 (15.3 % dermal absorption) ÷ 70 kg bw = 0.0082 mg/kg bw/day.

MOE = NOAEL ÷ ADD then 1.25 mg/kg bw/day ÷ 0.0082 mg/kg bw/day = **152.**

Since the MOE is > 100, the proposed use does not exceed ARIA/RDs level of concern under these application parameters.

RESTRICTED ENTRY INTERVAL (REI)

Difenoconazole is classified in acute toxicity category III for acute dermal toxicity and primary eye irritation. It is classified in Toxicity Category IV for acute inhalation toxicity and primary skin irritation. It is negative as a dermal sensitizer. Therefore, the interim worker protection standard (WPS) REI of 12 hours is adequate to protect agricultural workers from a most of post-application exposures to difenoconazole. The draft Inspire® label lists the REI as 12 hours. Post-application exposure to floricultural crops treated at the highest rate of application results in residues of concern thus an extended REI is necessary for that use pattern.

ATTACHMENT

3.4.12 Summary of Toxicological Doses and Endpoints for Difenoconazole for Use in Human-Health Risk Assessments

Table 3.4.12a Summary of Toxicological Doses and Endpoints for Difenoconazole for Use in Dietary and Non-Occupational Human Health Risk Assessments.

Exposure Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, LOC for Risk Assessment	Study and Relevant Toxicological Effects
Acute Dietary (All populations)	NOAEL = 25 mg/kg	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	aRfD = aPAD = 0.25 mg/kg/day	**Acute Neurotoxicity Study in Rats** LOAEL= 200 mg/kg in males based on reduced fore-limb grip strength in males on day 1.
Chronic Dietary (All populations)	NOAEL = 0.96 mg/kg/day	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	cRfD = cPAD = 0.01mg/kg/day	**Combined chronic toxicity/carcinogenicity (rat; dietary)** LOAEL = 24.1/32.8 mg/kg/day (M/F) based on cumulative decreases in body weight gains
Incidental Oral Short- and Intermediate-Term (1-30 days and 1-6 months)	NOAEL = 1.25 mg/kg/day	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	Residential LOC for MOE<100	**Reproduction and fertility effects (rat; dietary)** Offspring LOAEL = 12.5 mg/kg/day based on reduction in body weight of F_1 males
Dermal Short- and Intermediate-Term (1-30 days and 1-6 months)	Oral NOAEL = 1.25 mg/kg/day Dermal Absorption factor=15.3%	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	Residential LOC for MOE<100	**Reproduction and fertility effects (rat; dietary)** Offspring LOAEL = 12.5 mg/kg/day based on reduction in body weight gain of F_0 females prior to mating, gestation and lactation
Dermal Long-Term (>6 months)	Oral NOAEL = 0.96 mg/kg/day Dermal Absorption factor=15.3%	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	Residential LOC for MOE<100	**Combined chronic toxicity/carcinogenicity (rat; dietary)** LOAEL = 24.1/32.8 mg/kg/day (M/F) based on cumulative decreases in body weight gains
Inhalation (Short- and Intermediate-term)	Oral NOAEL = 1.25 mg/kg/day 100% inhalation absorption assumed	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	Residential LOC for MOE<100	**Reproduction and fertility effects (rat; dietary)** Offspring LOAEL = 12.5 mg/kg/day based on reduction in body weight gain of F_0 females prior to mating, gestation and lactation
Inhalation	Oral NOAEL	UF_A = 10X	Residential LOC for	**Combined chronic**

Table 3.4.12a Summary of Toxicological Doses and Endpoints for Difenoconazole for Use in Dietary and Non-Occupational Human Health Risk Assessments.				
Exposure Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD, LOC for Risk Assessment**	**Study and Relevant Toxicological Effects**
(Long- term)	= 0.96 mg/kg/day 100% inhalation absorption assumed	UF_H = 10X UF_{FQPA} = 1X	MOE<100	**toxicity/carcinogenicity (rat; dietary)** LOAEL = 24.1/32.8 mg/kg/day (M/F) based on cumulative decreases in body weight gains
Cancer (oral, dermal, inhalation)	Difenoconazole is classified as a Group C, possible human carcinogen with a non-linear (MOE) approach for human risk characterization (CPRC Document, 7/27/94, Memo, P. V. Shah dated March 3, 2007, HED Doc. No. 0054532)			

Abbreviations: UF = uncertainty factor, UF_A = extrapolation from animal to human (interspecies), UF_H = potential variation in sensitivity among members of the human population (intraspecies), UF_{FQPA} = FQPA Safety Factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, RfD = reference dose (a = acute, c = chronic), PAD = population adjusted dose, MOE = margin of exposure, LOC = level of concern.

Table 3.4.12b Summary of Toxicological Doses and Endpoints for Difenoconazole for Use in Occupational Human Health Risk Assessments				
Exposure Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short- and Intermediate-Term (1-30 days and 1-6 months)	Oral NOAEL = 1.25 mg/kg/day Dermal Absorption factor=15.3%	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	Occupational LOC for MOE<100	**Reproduction and fertility effects (rat; dietary)** Offspring LOAEL = 12.5 mg/kg/day based on reduction in body weight gain of F_0 females prior to mating, gestation and lactation
Dermal Long-Term (>6 months)	Oral NOAEL = 0.96 mg/kg/day Dermal Absorption factor=15.3%	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	Occupational LOC for MOE<100	**Combined chronic toxicity/carcinogenicity (rat; dietary)** LOAEL = 24.1/32.8 mg/kg/day (M/F) based on cumulative decreases in body weight gains
Inhalation (Short- and Intermediate-term)	Oral NOAEL = 1.25 mg/kg/day 100% inhalation absorption assumed	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	Occupational LOC for MOE<100	**Reproduction and fertility effects (rat; dietary)** Offspring LOAEL = 12.5 mg/kg/day based on reduction in body weight gain of F_0 females prior to mating, gestation and lactation
Inhalation (Long- term)	Oral NOAEL = 0.96 mg/kg/day 100% inhalation absorption	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	Occupational LOC for MOE<100	**Combined chronic toxicity/carcinogenicity (rat; dietary)** LOAEL = 24.1/32.8 mg/kg/day (M/F) based on cumulative decreases in

Table 3.4.12b Summary of Toxicological Doses and Endpoints for Difenoconazole for Use in Occupational Human Health Risk Assessments				
Exposure Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
	assumed			body weight gains
Cancer (oral, dermal, inhalation)	Difenoconazole is classified as a Group C, possible human carcinogen with a non-linear (MOE) approach for human risk characterization (CPRC Document, 7/27/94, Memo, P. V. Shah dated March 3, 2007, HED Doc. No. 0054532)			

Abbreviations: UF = uncertainty factor, UF_A = extrapolation from animal to human (interspecies), UF_H = potential variation in sensitivity among members of the human population (intraspecies), UF_{FQPA} = FQPA Safety Factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, RfD = reference dose (a = acute, c = chronic), PAD = population adjusted dose, MOE = margin of exposure, LOC = level of concern

Summaries of toxicological endpoints for use in risk assessment provided in personal communication (e-mail) from P. V. Shah, RAB1 Acting Branch Chief, 19 July 2007.

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Chemical: Difenoconazole

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